PCT/EP 99/06433

09/786435

Europäisches Patentamt | European Patent Office | Office européen des brevets

EP 99/06433

Bescheinigung Certificate Attestation

Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein.

The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. Patent application No. Demande de brevet n°

98116692.9

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

Der Präsident des Europäischen Patentamts:
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

I.L.C. HATTEN-HECKMAN

DEN HAAG, DEN
THE HAGUE,
LA HAYE, LE 13/10/99

Europäisches Patentamt
European Patent Office
Office européen des brevets

Blatt 2 der Bescheinigung
Sheet 2 of the certificate
Page 2 de l'attestation

Anmeldung Nr.:
Application no.:
Demande n°: 98116692.9

Anmeldetag:
Date of filing:
Date de dépôt: 03/09/98

Anmelder:
Applicant(s):
Demandeur(s):
BIOPHARM GESELLSCHAFT ZUR BIOTECHNOLOGISCHEN ENTWICKLUNG VON PHARMAKA mbH
69115 Heidelberg
GERMANY

Bezeichnung der Erfindung:
Title of the invention:
Titre de l'invention:
Use of TGF-inhibitors for treating cerebral disorders

In Anspruch genommene Priorität(en) / Priority(ies) claimed / Priorité(s) revendiquée(s)

Staat: State: Pays:	Tag: Date: Date:	Aktenzeichen: File no. Numéro de dépôt:

Internationale Patentklassifikation:
International Patent classification:
Classification internationale des brevets:
/

Am Anmeldetag benannte Vertragstaaten:
Contracting states designated at date of filing: AT/BE/CH/CY/DE/DK/ES/FI/FR/GB/GR/IE/IT/LI/LU/MC/NL/PT/SE
Etats contractants désignés lors du depôt:

Bemerkungen:
Remarks:
Remarques:

Applicant: Biopharm Gesellschaft zur biotechnologischen Entwicklung von Pharmaka mbH

Our Ref: B 1887EU - py / wa

Description

The present invention relates to the use of a compound capable of substantially inhibiting the biological activity of TGF-β on predamaged neurones, for treating cerebral disorders, and to pharmaceutical compositions containing said compound and a second compound for disintegrating blood clots.

The transforming growth factor β (TGF-β) family contains subspecies TGF-β1, TGF-β2 and TGF-β3, which are widely distributed and contextually acting cytokines with prominent roles in development and cell cycle control. TGFβs have been implicated in the regulation of neuronal survival of e.g. motoneurones, sensory and midbrain dopaminergic neurones.

Cerebral disorders such as a neurodegenerativ disorder or cerebral ischemiae, result in injury or death of neurones in mammals, and produce motor and/or cognitive deficits that are often permanent. At present, in most of these cerebral disorders there is no treatment that reliable improves the prognosis of a patient suffering on said disorders.

Thus, the technical problem underlying the present invention is to provide a new system imparting protection and therefore survival on predamaged or injured neurones upon a certain cerebral disorder.

The solution of the above technical problem is achieved by providing the embodiments characterized in the claims.

In particular, the present invention is based on the fact that, beside promoting intact neurones, TGF-β the major regulator for the execution of predamaged

neurones upon a certain cerebral disorder. Accordingly, the present invention relates to the use of a compound capable of substantially inhibiting the biological activity of TGF-β on predamaged neurones, for treating cerebral disorders in mammals, preferably in man. The term "TGF-β" comprises the subspecies TGF-β1, TGF-β2, and TGF-β3.

In a preferred embodiment of the present invention the term "compound capable of substantially inhibiting the biological activity of TGF-β on predamaged neurones" refers to polyclonal or monoclonal antibodies directed to TGF-β, as TGFG-β inhibitors as well as to low molecular compounds such as chemical or non-proteinaceous compounds, as TGF-β-antagonists.

The cerebral disorder includes peripheral and/or CNS-disorders including cerebral and focal ischemiae such as apoplexy, and neurodegenerative disorders such as ALS. For example, adverse consequences of central nervous system injuries may be caused by thrombus, embolus, systemic hypotension, hypertension, hypertensive cerebral vascular disease, rupture of an aneurysm, an angioma, blood dyscrasias, cardiac failure, cardic arrest, cardiogenic shock, septic shock, head trauma, spinal cord trauma, seizure, bleeding from a tumor, or other blood loss. The spiral cord, which is also a part of the central nervous system, is equally susceptible to ischemia resulting from diminished blood flow.

Where the ischemia is associated with a "stroke", it can be either global or focal ischemia, as defined below.

By "focal ischemia", as used herein in reference to the central nervous system, is meant the condition that results from the blockage of a single artery that supplies blood to the brain or spinal cord, resulting in the death of all cellular elements (pan-necrosis) in the territory supplied by that arterty.

By "global ischemia", as used herein in reference to the central nervous system, is meant the condition that results from a general diminution of blood flow to the entire brain, forebrain, or spinal cord, which causes the death of neurons in

selectively vulnerable regions throughout these tissues. The pathology in each of these cases is quite different, as are the clinical correlates. Models of focal ischemia apply to patients with focal cerebral infarction, while models of global ischemia are analogous to cardiac arrest, and other causes of systemic hypotension.

A further aspect of the present invention relates to a pharmaceutical composition containing, in pharmaceutically effect amounts, the above defined compound, and a second compound for disintegrating blood clots, and optionally a pharmaceutically acceptable carrier and/or diluent. In a preferred embodiment of the present invention, the second compound is selected from the group consisting of urokinase, thrombin, and tPA (tissue plasminogen activator).

The treatment regimen is carried out, in terms of administration mode, timing of the administration, in dosage, so that the functional recovery of the patient from the adverse consequence of the cerebral disorder is improved.

The administration of the compound or pharmaceutical composition according to the present invention can be carried out by any standard route and known rule of administration, including intravenously, orally, or intracerebrally. The dosage of such antibodies or antagonists according to the present invention lies preferably within a range of circulating concentrations that include the ED_{50} with little or no toxicity. The dosage can vary within this range depending upon the dosage form employed and the route of administration utilized.

The formulation of the above defined compound or the pharmaceutical composition according to the present invention does not exhibit any specific restriction, and may be prepared e.g. in the form of tablets, suppositories, solutions, or retarded release-formulations. The antibodies or antagonists for example can be formulated for parenteral administration by injection, for example, by bolus injection or continuous infusion. Formulations for injection can be presented in unit dosage form, for example, in ampules or in multi-dose containers, with an added preservative.

The therapeutic antibodies or antagonists of the invention can also contain a carrier or excipient and/or diluent, many of which are known to skilled artisans. Excipients which can be used include buffers (for example, citrate buffer, phosphate buffer, acetate buffer, and bicarbonate buffer), amino acids, urea, alcohols, ascorbic acid, phospholipids, proteins (for example, serum albumin), EDTA, sodium cholride, liposomes, mannitol, sorbitol, and glycerol.

It is well known in the medical arts that dosages for any one patient depend on may factors, including the general health, sex, weight, body surface area, and age of the patient, as well as the particular compound to be administered, in the time and route of administration, and other drugs being administered concurrently. Determining the most appropriate dosage and route of administration is well within the abilities of a skilled physician.

CLAIMS

1. Use of a compound capable of substantially inhibiting the biological activity of TGF-β on predamaged neurones, for the preparation of a medicament for treating cerebral disorders.

2. Use according to claim 1, wherein said compound is an antibody directed to TGF-β.

3. Use according to claim 1 or 2, wherein said disorder is a peripheral and/or CNS-disorder.

4. Use according to claim 3, wherein said disorder is a cerebral ischemia or a neurodegenerative disorder.

5. A pharmaceutical composition containing, in pharmaceutically effective amounts, a compound capable of substantially inhibiting the biological activity of TGF-β on predamaged neurones, and a second compound for disintegrating blood clots, and optionally a pharmaceutically acceptable carrier and/or diluent.

6. The pharmaceutical composition according to claim 5, wherein said compound is an antibody directed to TGF-β.

7. The pharmaceutical composition according to claim 5 or 6, wherein said second compound is selected from the group consisting of urokinase, thrombin, and tissue plasminogen activator.

ABSTRACT

The present invention relates to the use of a compound capable of substantially inhibiting the biological activity of TGF-β on predamaged neurones, for treating cerebral disorders, and to pharmaceutical compositions containing said compound and a second compound for disintegrating blood clots.